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(54) Title: OCCLUSION RESISTANT HYDROCEPHALIC SHUNT

(57) Abstract: An occlusion resistant medical shunt, particularly a hydrocephalic shunt, is provided for implantation into a mammal. The shunt has an elongate wall structure configured as a tube having a lumen therethrough and a proximal end for receipt of bodily fluids. The bodily fluids, such as cerebrospinal fluid, flows through the shunt to a distal end for discharge of the bodily fluids. The wall structure of the shunt generally includes a biocompatible medical device material. The shunts of the present invention further include one or more occlusion resistant materials to resist occlusion of the lumenal passage in the shunt.

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OCCLUSION RESISTANT HYDROCEPHALIC SHUNT

FIELD OF THE INVENTION

This invention relates to cerebrospinal fluid shunts and techniques to prevent blockage or occlusion of such a shunt.

BACKGROUND OF THE INVENTION

Hydrocephalic shunts are designed to remove excess fluid from the ventricular region of the brain to a different internal location, such as the peritoneal cavity. Alternatively, cerebral spinal fluid (CSF) shunts may have a proximal end placed into the patient's ventricular region and a distal end being connected external of the patient. In either configuration, a common problem involves the immune response of the patient or inflammatory response to the insertion of the foreign body, i.e., the catheter, therein. Additionally, occlusion of the catheter lumens often occur and preclude effective drainage of the CSF fluid. It is estimated that 40% of implanted hydrocephalic shunts fail after 5 years due to tissue proliferation into the shunt lumen.

U.S. Patent No. 6,110,155, issued to Baudino, and commonly owned by Applicant of the present application, shows an anti-inflammatory agent loaded catheter distal tip and method for preventing tissue fibrosis. The device and method utilizes, in one embodiment, dexamethasone sodium phosphate agent on a ventricular catheter tip to prevent encapsulation of the catheter. U.S. Patent No. 6,348,042 B1, issued to Warren, Jr., discloses a bio-active shunt device and method by which the interior lumen surface of a shunt is coated with a matrix forming system having at least one enzyme configured for inciting activity to preclude the growth of obstructing cellular material. In one embodiment, the interior surface of the catheter lumen is impregnated with proteases or a matrix containing proteases that is impregnated onto the wall of the lumen to degrade cellular material including cells of the choroid plexus and peritoneum. U.S. Patent No. 4,655,645, issued to Corbett, discloses a mechanical method and technique for preventing ingrowth into a ventricular catheter by brain tissue, e.g., the choroid plexus.

U.S. Patent No. 5,282,844, issued to Stokes, et al., and also commonly owned by Applicant of the present invention, discloses use of steroid eluting pacing lead electrodes for cardiology applications. Other references are known to discuss a range of drug eluting devices, including stents designed to contact tissue with fully coated drug eluding surfaces. All of these references fail to disclose the novel and non-obvious combinations as disclosed herein.

Figure 8 through 13 are cross-sectional views of various locations of occlusion resistant materials on a shunt catheter.

Figure 14 is a graph of drug release data from a catheter prepared by varying solvent and drug concentration.

Figure 15 is a graph of drug release data from a catheter prepared by a dip-coating method.

Figure 16 is a graph of drug release data from a catheter prepared by a barrier layer method.

Figure 17 is a graph of drug release data from a catheter with additive modulated methods.

Figure 18 is a graph of drug release data from a catheter prepared with drug loading by extrusion process and shows cytokine release from activated from human cells in the presence of silicon and several dexamethasone concentrations.

Figure 19 is a graph of drug release data from an immunosuppressant.

Figure 20 is a graph of drug release data from an immunosuppressant.

Figure 21 is a graph of drug release data from an anti-proliferative.

Figure 22 is a graph of drug release data from an anti-proliferative.

Figure 23 is a graph of drug release data from an anti-neoplastic.

Figure 24 is a graph of drug release data from an anti-neoplastic.

Figure 25 is a graph of drug release data from an immunosuppressant in a catheter.

Figure 26 is a graph of drug release data from an immunosuppressant in a shunt.

Figure 27 is a graph of drug release data from an immunosuppressant in a catheter.

Figure 28 is a graph of drug release data from an immunosuppressant in a catheter.

Figure 29 is a graph of drug release data from an immunosuppressant in a catheter with a silicone plug.

DETAILED DESCRIPTION OF THE INVENTION

Shunts for treatment of hydrocephalus are well known and have evolved over many decades. Although many cases of obstructive hydrocephalus are treated successfully with endoscopic fenestration of the floor of the third ventricles, there are also many types of hydrocephalus and hydrocephalic patients which require shunting. Typically, a hydrocephalic shunt includes a tubing with a proximal end located in the brain tissue and a distal end located either within the patient at another location external to the

A shunt may be occluded at three different locations. First, at an entry point such as the proximal location in the brain, second, at the level of the valve system, commonly referred to as a "valve obstruction", and third, at the level of the distal end, referred to as a distal catheter occlusion. The focus of this invention relates to either distal or proximal occlusions rather than valve obstructions, although valve obstructions may be a sequelae of occlusions or infection migrating from the distal or proximal ends.

Proximal occlusions are more common than distal occlusions, and often result from blood or cellular debris which block the lumen and distal holes on ventricular catheters. This growth may depend on artificial properties (chemistry and geometry) as well as the distance between catheter and tissues in the ventricular (catheter positioning and slit ventricles syndrome). Some ventricular catheter tip designs have been proposed for maintaining the holes of the ventricular catheter away from the walls of the ventricles and the choroids plexus in order to resolve this problem. However, these devices are likely unable to fully prevent proximal occlusion from occurring. Moreover, those known as flanged catheters actually promote firm attachment of the catheter tubing to the choroids plexus. Although distal obstructions are not as frequent as that at the proximal end, shunt-type catheters can be obstructed in the peritoneal cavity by ingrowth of mesothelial cells and fibroblasts.

The inventors have recognized this phenomenon and have developed solutions which go beyond that currently known or suggested. Figure 1 shows one embodiment of the hydrocephalic or CSF shunt 10 of the present invention, wherein the shunt 10 includes an elongated conduit 11 having a proximal portion 12, one or more valves 14, a central portion 16, and a distal portion 18. The elongated conduit 11 may be of any shape or size, but generally will be in the form of a tube made of an elastomeric material. As noted above, proximal portion 12 is placed in the patient's head at the region of the ventricles while the central portion 16 is routed subcutaneously along the patient's neck and torso. The distal portion 18 may be placed for drainage of the cerebral spinal fluid into the peritoneal cavity where the fluid is then reabsorbed by the normal bodily processes or may extend out of the patients body for external drainage.

It is evident that the proximal and distal portions 12,18 reside in different bodily environments, with different challenges to functionality. In the brain, where the majority

following list provides additional examples of anti-occlusion agents that may be utilized in the present invention.

Anti-inflammatory- cortisone, hydrocortisone, prednisone, dexamethasone, methylprednisolone and their derivatives.

Non-steroidal anti-inflammatory agents including their racemic mixtures or individual enantiomers where applicable- ibuprofen, flurbiprofen, ketoprofen, aclofenac, diclofenac, aloxiprin, aproxen, aspirin, diflunisal, fenoprofen, indomethacin, mefenamic acid, naproxen, phenylbutazone, piroxicam, salicylamide, salicylic acid, sulindac, desoxysulindac, tenoxicam, tramadol, ketoralac, flufenisal, salsalate, triethanolamine salicylate, aminopyrine, antipyrine, oxyphenbutazone, apazone, cintazone, flufenamic acid, clonixerl, clonixin, meclofenamic acid, flunixin, coichicine, demecolcine, allopurinol, oxypurinol, benzydamine hydrochloride, dimefadane, indoxole, intrazole, mimbane hydrochloride, paranylene hydrochloride, tetrydamine, benzindopyrine hydrochloride, fluprofen, ibufenac, naproxol, fenbufen, cinchophen, diflumidone sodium, fenamole, flutiazin, metazamide, letimide hydrochloride, nexeridine hydrochloride, octazamide, molinazole, neocinchophen, nimazole, proxazole citrate, tesicam, tesimide, tolmetin, and triflumidate;

Antineoplastic/antiangiogenic- antimetabolite agents, alkylating agents, cytotoxic antibiotics, vinca alkaloids, mitosis inhibitors, platinum compounds, tissue growth factor inhibitors, cisplatin and etoposide

Immunosuppressant agents - cyclosporine A, mycophenolic acid, tacrolimus, rapamycin, rapamycin analogue (ABT-578) produced by Abbott Laboratories, azathioprine, recombinant or monoclonal antibodies to interleukins, T-cells, B-cells and /or their receptors.

Antithrombogenic Factors- Anticoagulents, such as heparin and chondroiten sulfate; Platelet inhibitors such as ticlopidine; Vasodilators such as cyclandelate, isoxsuprine, papaverine, dipyrimadole, isosorbide dinitrate, phentolamine, nicotinyl alcohol, co-dergocrine, nicotinic acid, glycerl trinitrate, pentaerythritol tetranitrate and xanthinol; and Thrombolytic agents, such as stretokinase, urokinase and tissue plasminogin activators.

Antiproliferative agents- paclitaxel, actinomycin D, rapamycin, tacrolimus, everolimus, dexamethasone and rapamycin analogue (ABT-578) produced by Abbott Laboratories;

homoharringtonine, selenium compounds, superoxide-dismutase, interferons, heparin, analogs, homologs, and derivatives of the above group.

The agent 20 may be applied by a variety of suitable application methods, such as a dip-coating techniques, spray coating techniques or as an impregnation of the agents 20 into the material utilized to produce the shunt walls. Additionally, the anti-occlusion agents 20 may be included in other carrier materials (not shown) that allow for the release of the agents 20, such as polymeric coatings. Once the anti-occlusion agents 20 are included in the carrier materials they may be applied to the shunts of the present invention utilizing the techniques disclosed above (i.e. dip coating, spray coating, etc.). The polymers utilized in the present invention can be bioabsorbable polmers, biostable polymers or combinations thereof. Suitable bioabsorbable polymeric coatings that may be utilized in embodiments of the present invention include, but are not limited to, poly(L-lactic acid), poly(lactide-co-glycolide) and poly(hydroxybutyrate-co-valerate). Suitable biostable polymers include, but are not limited to silicones, polyurethanes, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers, polyethylene, polypropylene, polycarbonate, polysulfone and cellulosics. Other polymers that may be utilized in embodiments of the present invention include polydimethylsiloxanes, methylhydrosiloxane-dimethylsiloxane copolymers, polymethylhydrosiloxanes, polyethylhydrosiloxanes, hydride terminated polyphenyl-(dimethylhydrosiloxy)siloxanes, methylhydrosiloxane-phenylmethylsiloxane copolymers, N-vinylpyrrolidone/methyl methacrylate copolymers, 2-hydroxyethylacrylate (e.g. polymacon), various copolymers of 2-hydroxyethylmethacrylate (e.g. hafilcon A and B, vifilcon A, tetrafilcon, dimefilcon, bufilcon, perfilcon, etc.), copolymers of N-vinylpyrrolidone (e.g. lidofilcon A and B, scafilcon A, surfilcon, vifilcon, filcon YA, etc.), polyamides, polyimides, fluoropolymers, polytetrafluoroethylenes, natural rubber and polyisoprene.

Other embodiments of the present invention provide a cannula utilized in medical applications, such as a shunt 10, that includes an agent delivery device 23, such as spheres, cloth, inserts, eluting plugs, seeds, elongated members or other similar structures positioned in the drug eluting regions 21. Various embodiments that include one or more agent delivery devices 23 are depicted in Figures 8-13 and will be further explained below. The feature of matching the right agent 20 to the right drug eluting region 21 to prevent or

a rod or seed, centered by supports 40, or other means to stabilize and maintain the member 38 in the proximal portion 12 of the shunt 10.

Figure 5 is a section view of a proximal portion 12 of a CSF shunt 10 in which a pliable material 42 such as a cloth, fabric or membrane material is included in the lumen 28. The pliable material or foam 42 may be coated or loaded with an agent 20, such as dexamethasone or sirolimus, for delivery from the shunt 10. The pliable material 42 may be selected from any suitable material, such as a polyethylene terephthalate fabric, an expanded poly(tetrafluoroethylene) material, porous polypropylene fibers, porous polyurethane, porous silicone, or any other polymer or polymeric foam, or various combinations of these materials. It is recognized that other porous inert and biostable substrates and methods suitable for immobilizing an elutable occlusion-preventing agent may be used.

Figure 6 depicts a sectional view of another embodiment of the present invention wherein the proximal portion 12 of a CSF shunt 10 includes a plurality of inserts 44 adjoined to or incorporated into the wall structure 26 and adjacent to the apertures 24 of the proximal portion 12. The inserts may be integral to the wall structure or may be caps or plugs that interact with the wall structure ends near the apertures 24. Inserts 44 may be formed of any suitable material, such as a silicone rubber or other material and may be either coated or loaded with a radioactive or pharmaceutical agent 20, for example selenium or dexamethasone. This configuration focuses the occlusion preventing characteristics of the shunt 10 to the precise locations most affected. Figure 7 is a perspective view of one embodiment of an insert 44. The inserts 44 may be made into any form that facilitates its interaction with the shunt 10, such as in the form of CSF permeable caps, disks, tabs, tubes, cylinders, or plugs . It is again noted that the embodiments depicted in Figures 3-6 may be utilized at the proximal or distal portions 12, 18 of the shunt or selectively at other sites of the shunt.

Figures 8-13 are sectional views of further embodiments of proximal portions 12 of the present invention including one or more anti-occlusion agents 20 loaded onto or into the shunt 10. As previously mentioned in other embodiments, other portions of the shunt 10 depicted in Figures 8-13, such as the distal portion 18 or valve portion 14 may also include such drugs or anti-occlusion agents 20. Figure 8 depicts one embodiment of a proximal portion 12 of shunt 10 the wall structures 26 include fluid apertures 24 and a

homopolymers and copolymers, polyethers, polyamides, polyimides, fluoropolymers, polytetrafluoroethylenes, natural rubber and polyisoprene and cellulosics).

Figure 12 illustrates a drug loading using an impregnation approach. In one embodiment of the present invention the pharmaceutical agent 20 is dissolved in an organic solvent. Suitable organic solvents that may be utilized in the present application include, but are not limited to water, alcohols such as ethanol, methylene chloride, Xylene, Hexane, Acetone, Dimethyl Sulfoxide (DMSO), Tetrahydrofuran (THF) or combinations thereof. The amount of anti-occlusion agent added to the solvent is generally about 0.001 wt% to approximately 30 wt%, preferably about 0.05 wt% to about 5 wt% of the mixture. Next, the wall material 26 is immersed in the pharmaceutical saturated solvent thereby swelling and loading the material with pharmaceutical saturated solvent. As shown in Figure 12, only the portion of the shunt tubing which was immersed into the drug solution will be impregnated with drugs thereby forming the drug loaded tube portion 54.

Figure 13 depicts another example of drug distribution in a shunt 10, wherein an elastomeric material, such as silicone, and drug mixture is extruded to form a shunt 10. In contrast to an impregnation approach, shown in figure 12, an extrusion approach as depicted in Figure 13 may provide an optimum distribution of drug along the length of the extruded tubing. In such an embodiment the elastomeric material/drug mixture may include an amount of occlusion resistant agent, which is approximately 0.00001 wt% to about 20 wt%, preferably from about 0.001 wt% to about 1 wt % of the mixture. Once formed the elastomer/drug mixture may be extruded utilizing any extrusion device known in the art. It is recognized, however, that within the extrusion art it is possible to selectively configure extrusion steps and apparatus to further optimize by layer or location the drug distribution (or elution) rate, loading, and other characteristics.

Applicants have identified the value of having a CSF shunt proximal tip 22 with a first concentration of a drug 24 to interfere with tissue occlusion of the shunt 10 and a distal tip 30 having either no drug/agent, having the same drug/agent, or having a different concentration or a different drug/agent than the proximal tip 22. Also, a combination of agents 24 may be appropriate to protect patentcy of the shunt lumen 28 during the acute and chronic phases of the shunt implant. Combinations of drugs may also demonstrate different elution rates to achieve synergistic therapeutic outcomes not found or even expected otherwise. This, again, is a new approach to providing CSF shunts which are

throughout these examples to illustrate the effect of the drug's physical properties: dexamethasone phosphate (hydrophilic drug), dexamethasone free base (more hydrophobic than dexamethasone phosphate), dexamethasone acetate (most hydrophobic), and mycophenolic acid. By changing the method of drug loading, one skilled in the art can adjust drug release, as shown by drug releasing profiles used in the examples below.

Example 1. Drug loaded using an impregnation approach.

Standard shunt ventricular catheter silicone tubing (translucent, OD=0.083", ID=0.048"), made of platinum cured silicone rubber (Silastic MDX4-4210, Medical grade), was inserted into glass beakers containing solutions of Dexamethasone-acetate (DEX-Ac) in mixture, as specified in Table 1.

Table 1. DEX-Ac loading of 20mg weight pieces of shunts were made by placing each in 1g of the solution, composition of which is given in this table.

Sample	wt% DEX-AC	Xylene:Acetone
2	0.86	9:1 wt/wt
3	6.45	1:3 wt/wt
4	4.3	1:1 wt/wt

Samples were incubated at 40°C for 18.5h, following by rinsing with Xylene and drying in a vacuum oven for 28h. Samples were positioned in glass vials with a fixed amount of PBS buffer. Release test was done at 37°C in a 0.01M PBS buffer containing 0.138M NaCl and 0.0027M KCl using an incubator shaker (model C24 from New Brunswick Scientific Inc.), which was set up at 100 RPM. Drug release amount was estimated by UV-VIS test, performed at 240nm using 1 cm optical length quarts cuvette. Drug release kinetics are shown in Figure 14, with profile 151 correlating to Sample 2, and Samples 3 and 4 represented by Profiles 153, 154.

Tetrahydrofuran (THF) was used to obtain 200 volume % swelling of silicone rubber. Because most of the hydrophobic drugs are soluble in THF, this solvent can be an excellent candidate for loading hydrophobic drugs by swelling approach.

were adjusted to obtain the homogeneous mixture as verified by visual observation and low magnification optical microscopy. Silicone tubing was filled with this mixture using the proper size of syringe. It was done either manually or with an automated air dispenser system. Size of plug was visually controlled to be in a range of 3-4 mm.

Plugged tubes were cured at 150°C for 2 h followed by a weekend at room temperature. Drug release was measured as described in the above Example 1. The release profiles are given in Figure 16. In Figure 16, the sample abbreviation Ph20 at Profile 301 means that dexamethasone phosphate was mixed with silicone rubber at 20 wt% concentration of drug. Sample abbreviation Fb40-Ph5 at Profile 302 means that dexamethasone free base and dexamethasone phosphate were mixed with silicone rubber at concentrations of 40 wt% and 5 wt%, respectively. Sample abbreviation Fb22-Sb22 at Profile 303 means that dexamethasone free base and sodium bicarbonate were mixed with silicone rubber at concentrations of 22 wt% and 22 wt%, respectively. Profiles 304, 305, and 306 correspond using similar labeling methodology.

Example 6. Additives modulate drug release profile.

Sodium bicarbonate (Sb, Aldrich, pre-sieved to control the salt granule size) at concentration of 22 wt% or Tantalum powder (Ta, Aldrich) at concentrations between 10 wt% and 30 wt% were added to silicone/drug mixtures, described in the above Example 5, to modulate the dexamethasone release from the samples. Drug release was measured as described in Example 1. The release profiles are given in Figure 16 (curve Fb22-Sb22, Profile 303) and Figure 17. In Figure 17, the sample abbreviation Fb40-Ta20 at Profile 401 means that dexamethasone free base and tantalum powder were mixed with silicone rubber at concentrations of 40 wt% and 20 wt%, respectively. Profiles 402, 403, 404 and 405 are labeled using similar methodology.

Example 7. Drug loading by an extrusion process.

Dexamethasone free base was mixed at concentrations from 0.05 wt% to 0.1 wt% with raw ingredients of platinum cured rubber (Silastic MDX4-4210, Medical grade). The tubing (OD=2.1 mm; ID-1.1 mm) was extruded and cured according to a standard procedure, which involves a short-term (seconds) silicone/drug exposure to the elevated temperatures of around 200°C during the extrusion process. The drug released from this sample remained active after extrusion, as indicated in Figure 18 by the effect of the presence of the sample in the tubing with activated white blood cells. In this Figure, the

Mycophenolic acid was loaded in a silicone shunt by placing the distal part of the shunt in a 5 mg/ml solution of MPA in THF for 30 minutes at room temperature. After drying at room temperature for 24 hours, the samples were dip-coated with 11 wt % of RTV silicone in THF to form a barrier layer which reduces initial drug release. MPA release is shown at Profile 600 in a buffer in Figure 26.

Example 13. Immunosuppressive agent's release from catheter using dip-coating

MPA release from a silicone catheter dip coated into a PRS buffer is seen in Figure 27. Profiles 700, 701, 702, 703 and 704 designate the following dipping conditions, respectively: 33 Wt.% of MPA in solids; 20 Wt.% of MPA in solids; 10 Wt.% of MPA in solids; 5.0 Wt. % of MPA; 1.0 Wt. %. Total solids concentrations is 10 Wt.% in tetrahydrofuran dipping solution.

Example 14. Immunosuppressive agent's release from a catheter using a silicone plug

MPA release from silicone plugs into PRS buffer is seen in Figure 28. Profiles 801, 802 designate the following plug conditions, respectively: 10 wt.% MPA, 90% wt.% platinum cured rubber; 10 wt.% MPA, 30 wt.% sodium bicarbonate and 60 wt.% platinum cured rubber. Initial MPA loadings were 2.34 mg ±0.15 mg and 3.40 mg ± 0.11 mg for Profiles 801, 802, respectively.

Example 15. Anti-proliferative agent's loading into a shunt by impregnation followed by drug loading into a shunt plug

Rapamycin (RAPA) was loaded into a shunt by an impregnation process, according to which a distal part of a silicone shunt was placed in a 1 mg/ml solution of RAPA in THF for 30 minutes followed by drying at room temperature for 24 hours. Plugs were then made in a shunt using a platinum cured rubber, containing 0.1 wt % RAPA. These shunts were cleaned, packaged and ETO sterilized. Samples were then placed in a cell media for 4 hours. This media was added to an Astrocytoma cell culture, which resulted in a two fold inhibition of the cell growth, as compared to a fresh media.

Example 16. RAPA release from a shunt

Rapamycin (also named sirolimus) was loaded into a standard shunt catheter (called further peritoneal catheter) and into a downsized catheter (called further ventricular catheter). Ventricular catheters were 6 mm long with 2 mm silicone plug and 16 laser drilled holes. OD and ID of ventricular catheters were 0.30 mm and 0.65 mm

Example 18. In-vivo proof of the efficacy of a dual-drug release for mitigation of tissue proliferation

Ventricular and peritoneal samples were loaded with RAPA and MPA according to the following procedure: catheters were impregnated with 50 mg/ml of MPA solution in THF followed by plugging with 5 wt% RAPA in silicone Samples were implanted in rats and analyzed as described in the Example 17. Results are given in Table 1. Dual drug loading led to a stronger inhibition of the tissue proliferation if compared to a single drug loading.

Table 1. Tissue in-growth scores for MPA loaded and control samples.

	Drug free control	MPA loaded	MPA and RAPA loaded
peritoneal	4.03 ± 0.38	2.75 ± 0.53	2.20 ± 0.45
ventricular	3.03 ± 0.61	2.17 ± 0.51	1.48 ± 0.41

It was found that the combined release of drugs, as measured in-vitro after 2 months, was 30 micrograms for the ventricular catheter and 1080 micrograms for the peritoneal catheter.

Thus, embodiments of the occlusion resistant hydrocephalic shunt are disclosed. One skilled in the art will appreciate that the present invention can be practiced with embodiments other than those disclosed. The disclosed embodiments are presented for purposes of illustration and not limitation, and the present invention is limited only by the claims that follow.

microbials, nitric oxide donors, cell cycle inhibitors, anti-cancer agents, anti-arthritis agents, anti-diabetic agents, thrombin inhibitors, thrombolytics, antibiotics, antiviral agents, and gene therapy agents.

7. The occlusion resistant medical shunt of claim 6 wherein the occlusion-resistant material includes a material selected from the group consisting of beta-radiation emitting isotopes, dexamethasone, beclomethasone, cortisone, hydrocortisone, prednisone, methylprednisone, fluorometholone, tranilast, ketoprofen, curcumin, cyclosporin A, deoxyspergualin, FK506, sulindac, myriocin, 2-aminochromone (U-86983), colchicines, pentosan, antisense oligonucleotides, mycophenolic acid, paclitaxel, etoposide, actinomycin D, camptothecin, carmustine, methotrexate, adriamycin, mitomycin, cis-platinum, mitosis inhibitors, vinca alkaloids, tissue growth factor inhibitors, platinum compounds, cytotoxic inhibitors, alkylating agents, antimetabolite agents, tacrolimus, rapamycin, azathioprine, recombinant or monoclonal antibodies to interleukins, T-cells, B-cells, and receptors, bisantrene, retinoic acid, tamoxifen, compounds containing silver, doxorubicin, azacytidine, homoharringtonine, selenium compounds, superoxide-dismutase, interferons, heparin, rapamycin ABT-578 and analogs, homologs, derivatives or combinations of the above group.

8. The occlusion resistant shunt of claim 7 wherein the occlusion resistant material includes a material selected from the group consisting of mycophenolic acid, rapamycin, rapamycin ABT-578, derivatives or combinations thereof.

9. The occlusion resistant shunt of claim 7 wherein the occlusion resistant material includes mycophenolic acid.

10. The occlusion resistant shunt of claim 7 wherein the occlusion resistant material includes a combination of mycophenolic acid and, rapamycin or rapamycin ABT-578.

11. The occlusion resistant medical shunt of claim 1 wherein the occlusion-resistant material is distributed uniformly throughout the shunt.

12. The occlusion resistant medical shunt of claim 1 wherein the occlusion-resistant material is distributed only in drug eluting regions.

13. The occlusion resistant medical shunt of claim 12 wherein different occlusion-resistant materials are used in different drug eluting regions of the shunt.

14. The occlusion resistant medical shunt of claim 1 wherein the occlusion-resistant material is distributed in one or more agent delivery devices.

22. The occlusion resistant medical cannula of claim 20 wherein the elongated conduit comprises polyurethane material.

23. The occlusion resistant medical cannula of claim 18 wherein the occlusion-resistant material includes a material selected from the group of agents consisting of immunosuppressives, anti-inflammatories, anti-neoplastics, anti-angiogenics, anti-coagulants, anti-proliferatives, anti-thrombogenics, anti-oxidants, cyclooxygenase inhibitors, calcium entry blockers, anti-neoplastics, anti-mitotics, anti-microbials, nitric oxide donors, cell cycle inhibitors, anti-cancer agents, anti-arthritis agents, anti-diabetic agents, thrombin inhibitors, thrombolytics, antibiotics, antiviral agents, and gene therapy agents.

24. The occlusion resistant medical cannula of claim 23 wherein the occlusion-resistant material includes a material selected from the group consisting of beta-radiation emitting isotopes, dexamethasone, beclomethasone, cortisone, hydrocortisone, prednisone, methylprednisone, fluorometholone, tranilast, ketoprofen, curcumin, cyclosporin A, deoxyspergualin, FK506, sulindac, myriocin, 2-aminochromone (U-86983), colchicines, pentosan, antisense oligonucleotides, mycophenolic acid, paclitaxel, etoposide, actinomycin D, camptothecin, carmustine, methotrexate, adriamycin, mitomycin, cis-platinum, mitosis inhibitors, vinca alkaloids, tissue growth factor inhibitors, platinum compounds, cytotoxic inhibitors, alkylating agents, antimetabolite agents, tacrolimus, rapamycin, azathioprine, recombinant or monoclonal antibodies to interleukins, T-cells, B-cells, and receptors, bisantrene, retinoic acid, tamoxifen, compounds containing silver, doxorubicin, azacytidine, homoharringtonine, selenium compounds, superoxide-dismutase, interferons, heparin, rapamycin ABT-578 and analogs, homologs, derivatives or combinations of the above group.

25. The occlusion resistant medical cannula of claim 24 wherein the occlusion resistant material includes a material selected from the group consisting of mycophenolic acid, rapamycin, rapamycin ABT-578, derivatives or combinations thereof.

26. The occlusion resistant shunt of claim 25 wherein the occlusion resistant material includes mycophenolic acid.

27. The occlusion resistant shunt of claim 25 wherein the occlusion resistant material is a combination of mycophenolic acid and rapamycin or rapamycin ABT-578.

scafilcon A, surfilcon, vifilcon, filcon YA, etc.), polyamides, polyimides, fluoropolymers, polytetrafluoroethylenes, natural rubber and polyisoprene.

35. The method of preparing an occlusion resistant shunt of claim 32 wherein the elongated conduit comprises a silicone elastomer material.

36. The method of preparing an occlusion resistant shunt of claim 32 wherein the elongated conduit comprises polyurethane material.

37. The method of preparing an occlusion resistant shunt of claim 32 wherein the occlusion-resistant material includes a material selected from the group of agents consisting of immunosuppressives, anti-inflammatories, anti-neoplastics, anti-angiogenics, anti-coagulants, anti-proliferatives, anti-thrombogenics, anti-oxidants, cyclooxygenase inhibitors, calcium entry blockers, anti-neoplastics, anti-mitotics, anti-microbials, nitric oxide donors, cell cycle inhibitors, anti-cancer agents, anti-arthritis agents, anti-diabetic agents, thrombin inhibitors, thrombolytics, antibiotics, antiviral agents, and gene therapy agents.

38. The method of preparing an occlusion resistant shunt of claim 37 wherein the occlusion-resistant material includes a material selected from the group consisting of beta-radiation emitting isotopes, dexamethasone, beclomethasone, cortisone, hydrocortisone, prednisone, methylprednisone, fluorometholone, tranilast, ketoprofen, curcumin, cyclosporin A, deoxyspergualin, FK506, sulindac, myriocin, 2-aminochromone (U-36983), colchicines, pentosan, antisense oligonucleotides, mycophenolic acid, paclitaxel, etoposide, actinomycin D, camptothecin, carmustine, methotrexate, adriamycin, mitomycin, cis-platinum, mitosis inhibitors, vinca alkaloids, tissue growth factor inhibitors, platinum compounds, cytotoxic inhibitors, alkylating agents, antimetabolite agents, tacrolimus, rapamycin, azathioprine, recombinant or monoclonal antibodies to interleukins, T-cells, B-cells, and receptors, bisantrene, retinoic acid, tamoxifen, compounds containing silver, doxorubicin, azacytidine, homoharringtonine, selenium compounds, superoxide-dismutase, interferons, heparin, rapamycin ABT-578 and analogs, homologs, derivatives or combinations of the above group.

39. The method of preparing an occlusion resistant shunt of claim 38 wherein the occlusion resistant material includes a material selected from the group consisting of mycophenolic acid, rapamycin, rapamycin ABT-578, derivatives or combinations thereof.

51. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 50 wherein the shunt further includes at least one valve.

52. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 50 wherein the elongated conduit includes one or more elastomeric materials selected from the group consisting of poly(L-lactic acid), poly(lactide-co-glycolide), poly(hydroxybutyrate-co-valerate), silicones, polyurethanes, polyesters, vinyl homopolymers and copolymers, acrylate homopolymers and copolymers, polyethers, polyethylene, polypropylene, polycarbonate, polysulfone, cellulosics, polydimethylsiloxanes, methylhydrosiloxane-dimethylsiloxane copolymers, polymethylhydrosiloxanes, polyethylhydrosiloxanes, hydride terminated polyphenyl-(dimethylhydrosiloxy)siloxanes, methylhydrosiloxane-phenylmethylsiloxane copolymers, N-vinylpyrrolidone/methyl methacrylate copolymers, 2-hydroxyethylacrylate (e.g. polymacon), various copolymers of 2-hydroxyethylmethacrylate (e.g. hafilcon A and B, vifilcon A, tetrafilcon, dimefilcon, bufilcon, perfilcon, etc.), copolymers of N-vinylpyrrolidone (e.g. lidofilcon A and B, scafilcon A, surfilcon, vifilcon, filcon YA, etc.), polyamides, polyimides, fluoropolymers, polytetrafluoroethylenes, natural rubber and polyisoprene.

53. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 50 wherein the elongated conduit comprises a silicone elastomer material.

54. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 50 wherein the elongated conduit comprises polyurethane material.

55. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 50 wherein the occlusion-resistant material is selected from the group of agents consisting of immunosuppressives, anti-inflammatories, anti-neoplastics, anti-angiogenics, anti-coagulants, anti-proliferatives, anti-thrombogenics, anti-oxidants, cyclooxygenase inhibitors, calcium entry blockers, anti-neoplastics, anti-mitotics, anti-microbials, nitric oxide donors, cell cycle inhibitors, anti-cancer agents, anti-arthritis agents, anti-diabetic agents, thrombin inhibitors, thrombolytics, antibiotics, antiviral agents, and gene therapy agents.

56. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 55 wherein the occlusion-resistant material includes a material selected from the group consisting of beta-radiation emitting isotopes, dexamethasone, beclomethasone,

64. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 50 wherein the occlusion-resistant material is distributed in one or more agent delivery devices.

65. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 64 wherein the agent delivery devices are selected from the group consisting of spheres, cloth, inserts, eluting plugs, seeds, elongated members and combinations thereof.

66. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 50 wherein the occlusion-resistant material is distributed non-uniformly throughout the shunt and in different amounts.

67. The method of inhibiting the occlusion of an at least partially implanted shunt of claim 66 wherein the occlusion-resistant material is released at different rates between different portions of the shunt.

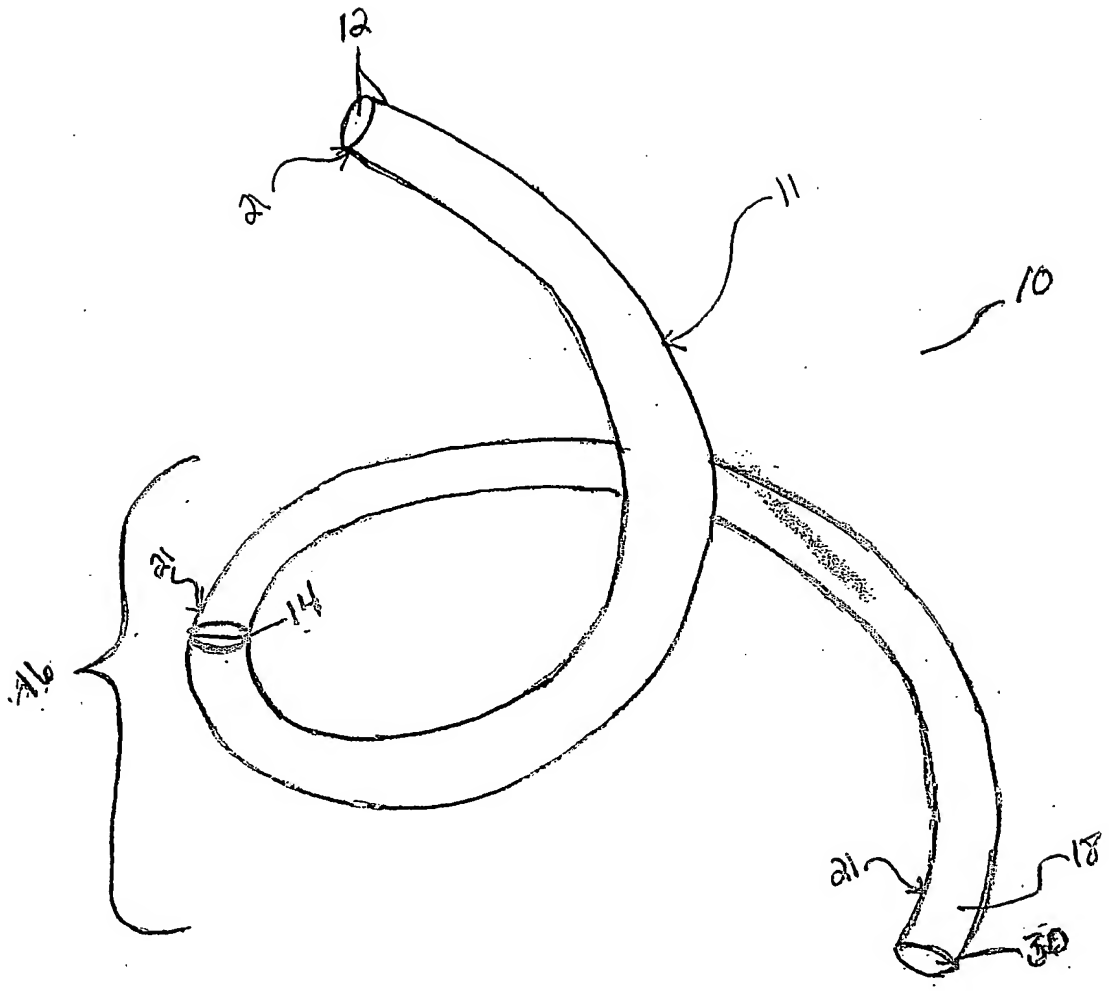


Fig. 1

FIG. 3

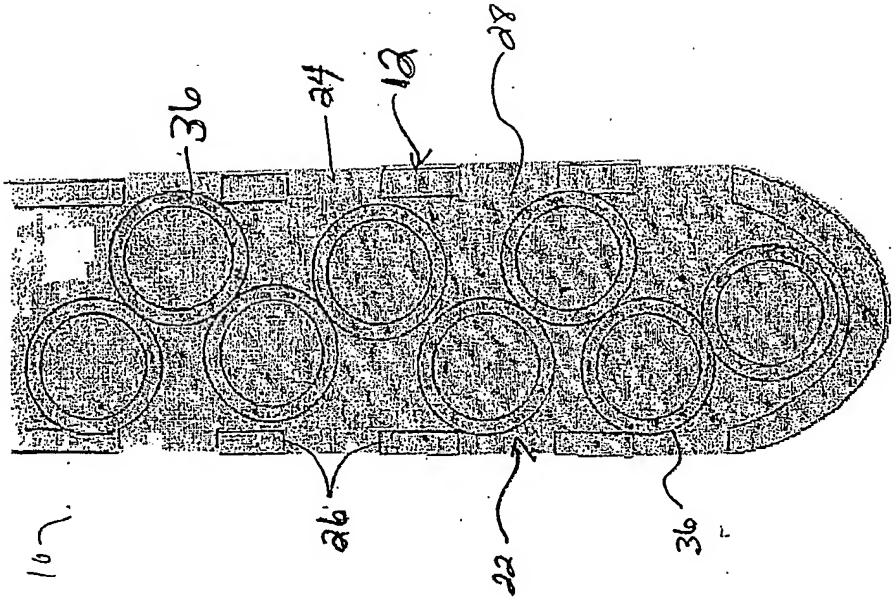

36
24
12
28
10
26
22
36

FIG. 2

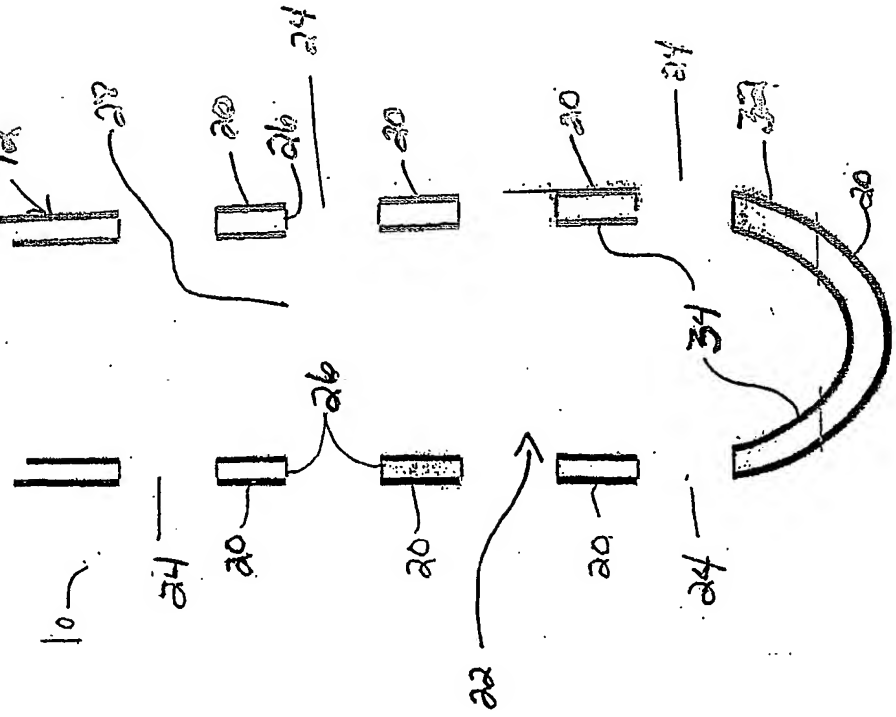

12
32
20
26
24
20
20
24
34
36
10
24
20
26
20
20
22
24
34
28

Fig. 5

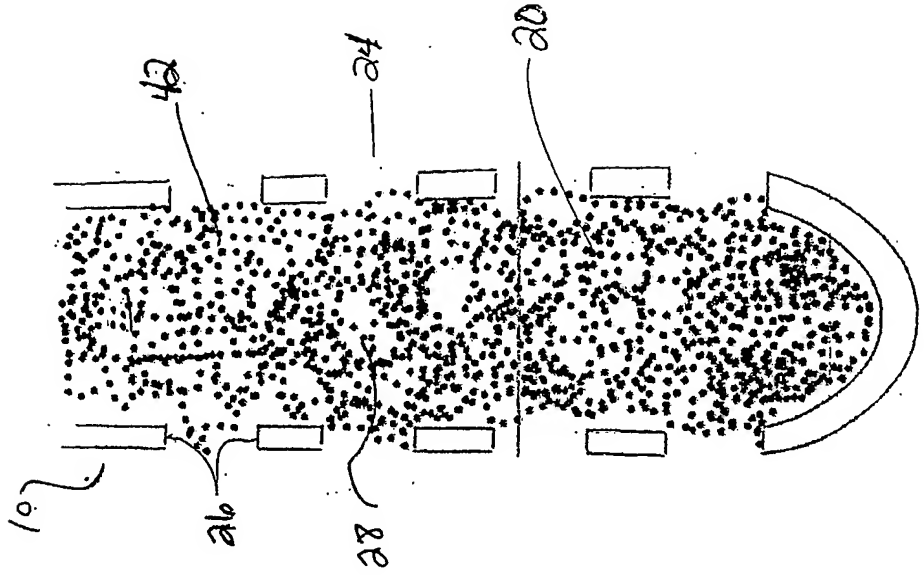


Fig. 4

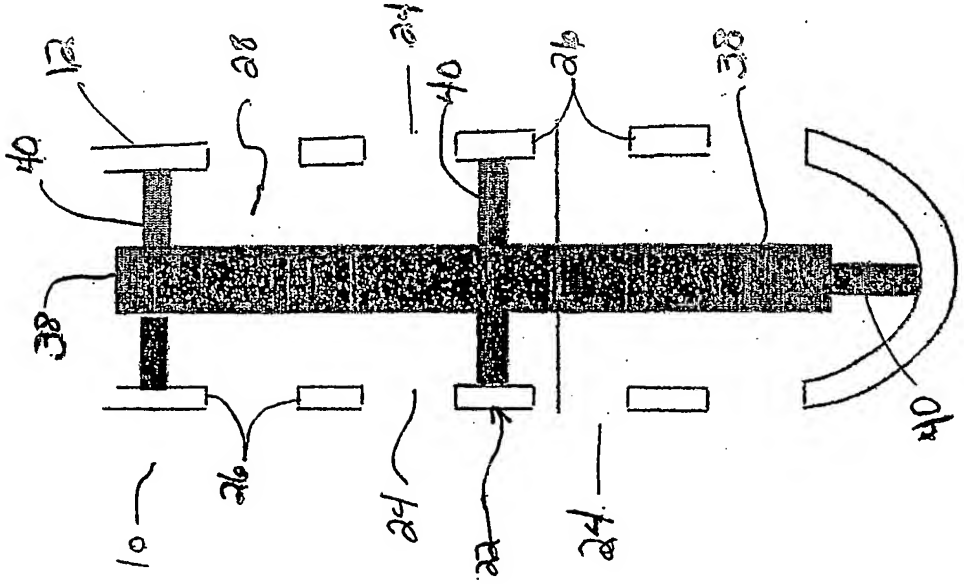
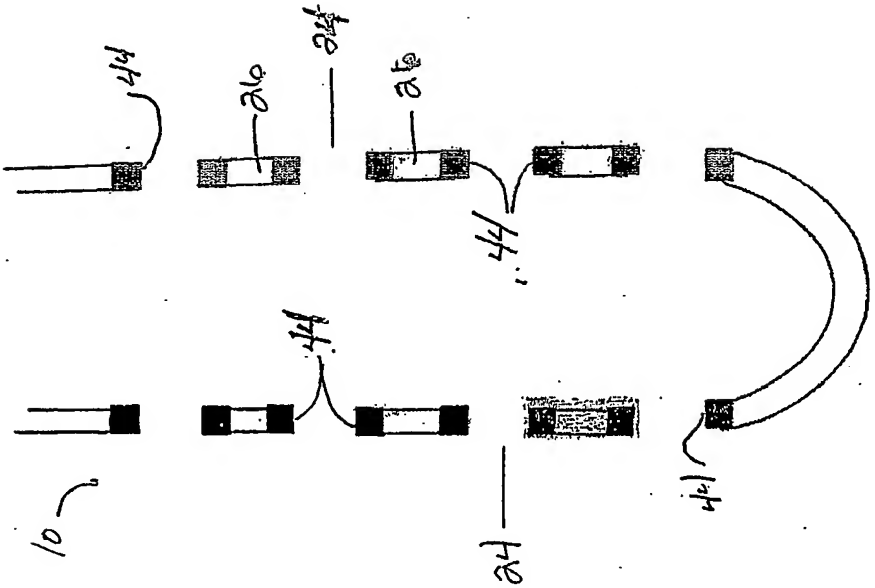


FIG. 7

FIG. 6



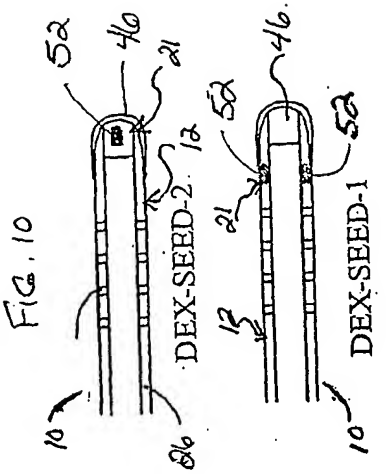


FIG. 10

FIG. 11

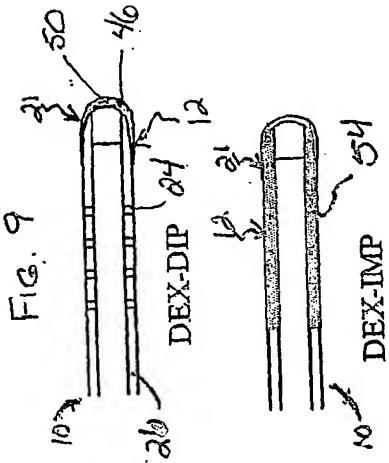


FIG. 9

FIG. 12

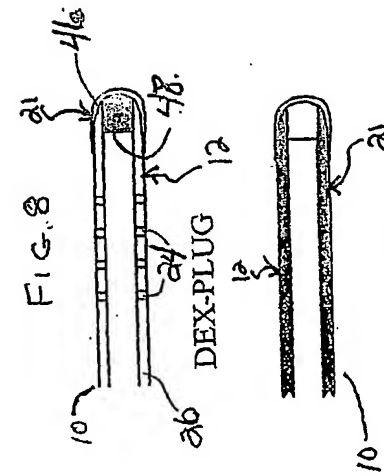


FIG. 8

FIG. 13

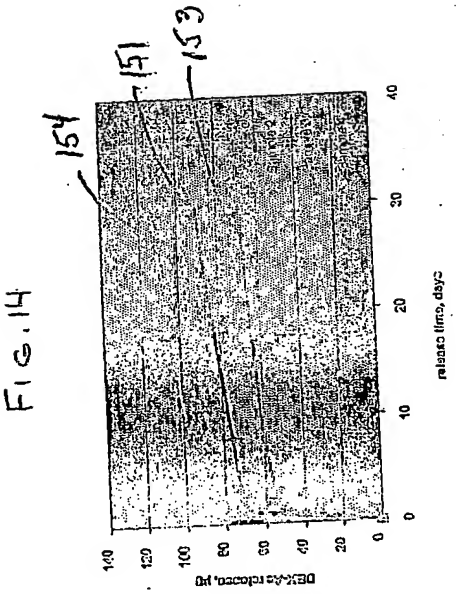


FIG. 14

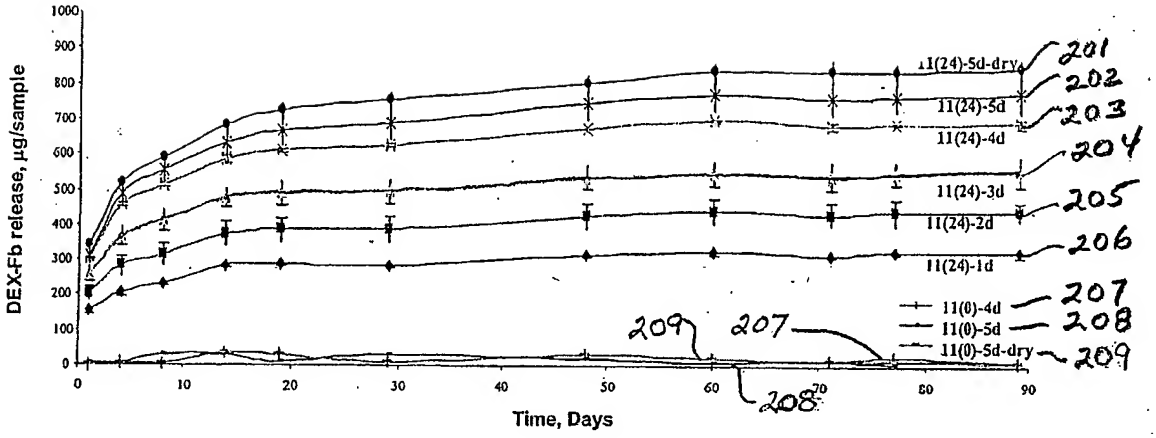
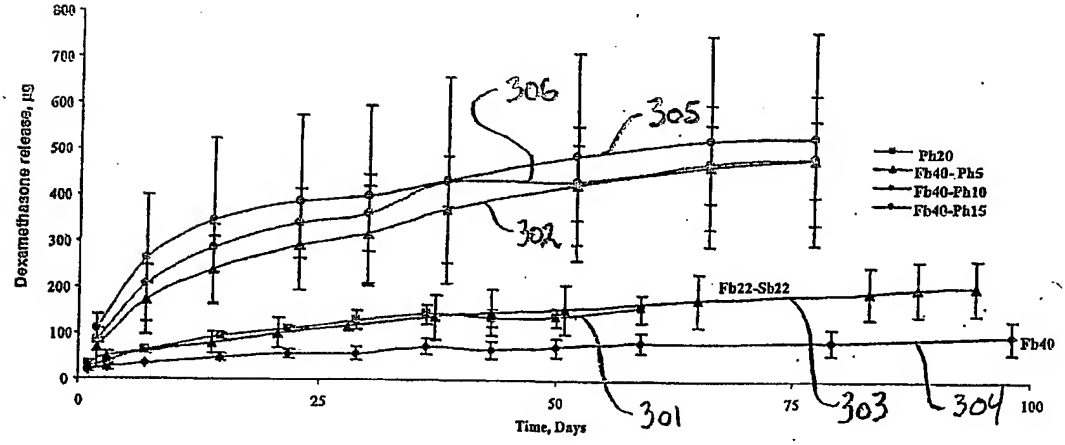

DEX-Fb release, µg/sample
Time, Days
11(24)-5d-dry
11(24)-5d
11(24)-4d
11(24)-3d
11(24)-2d
11(24)-1d
11(0)-4d
11(0)-5d
11(0)-5d-dry
201
202
203
204
205
206
207
208
209

FIG. 16


Dexamethasone release, µg
Time, Days
Ph20
Fb40-Ph5
Fb40-Ph10
Fb40-Ph15
Fb22-Sb22
Fb40
301
302
303
304
305
306

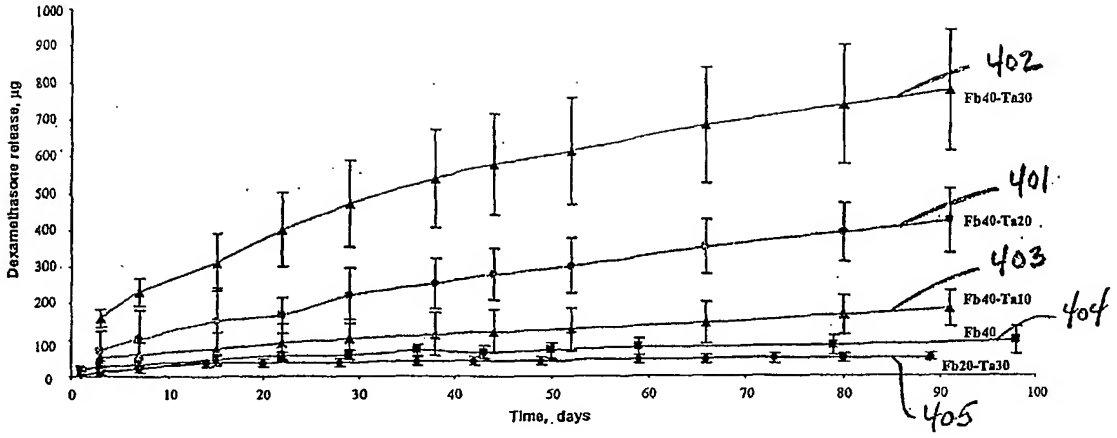

Dexamethasone release, µg
Time, days
Fb40-Ta30
Fb40-Ta20
Fb40-Ta10
Fb40
Fb20-Ta30
402
401
403
404
405

FIG. 18

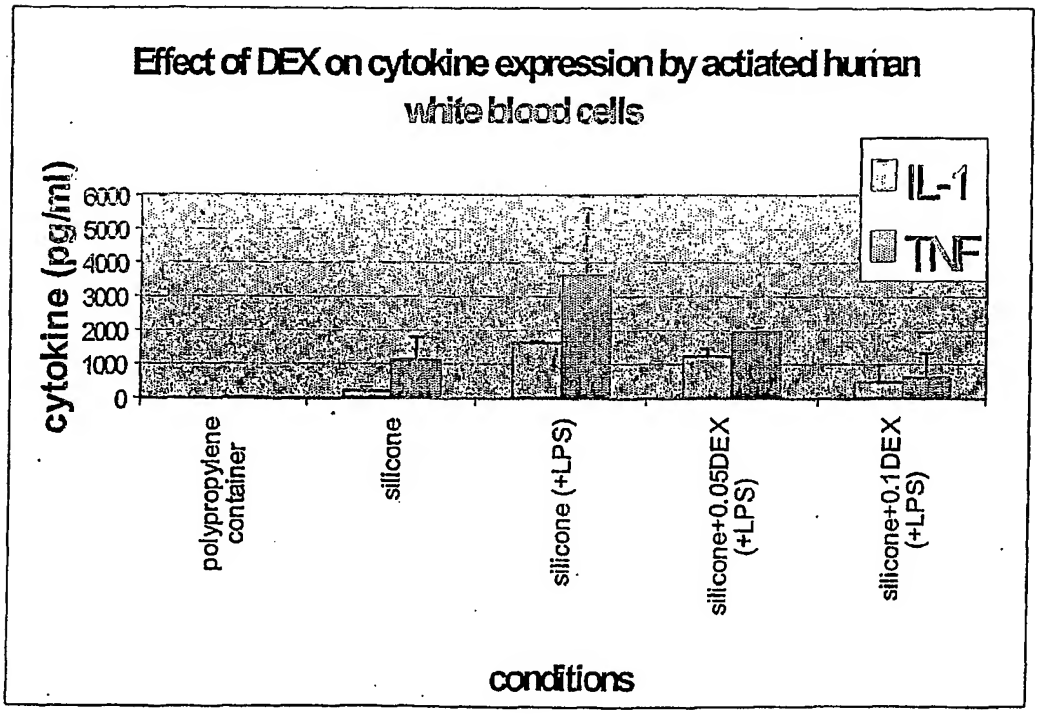

Effect of DEX on cytokine expression by actiated human white blood cells
cytokine (pg/ml)
IL-1
TNF
polypropylene container
silicone
silicone (+LPS)
silicone+0.05DEX (+LPS)
silicone+0.1DEX (+LPS)
conditions

FIG. 19

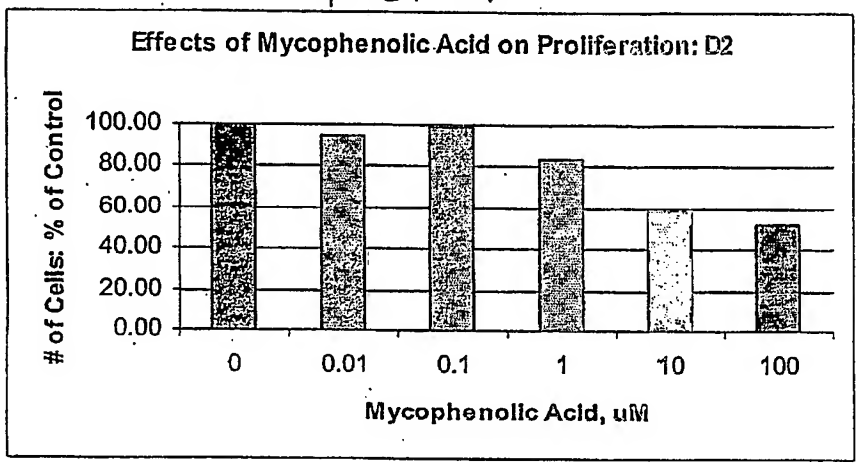


FIG. 20

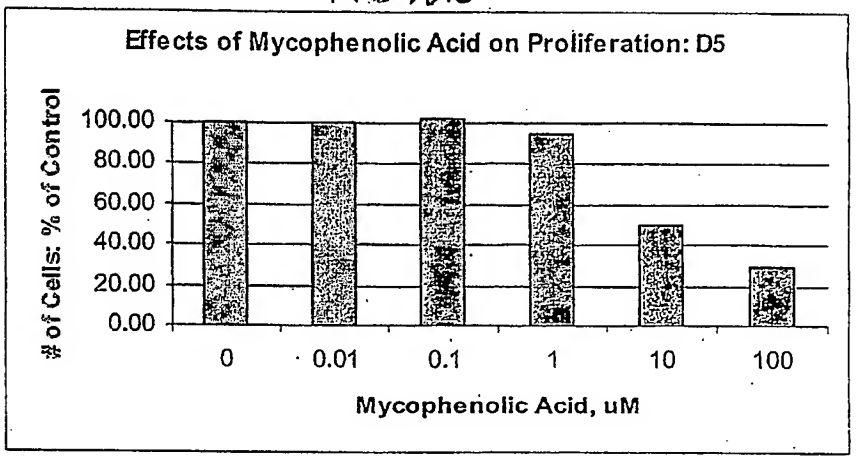


FIG. 21

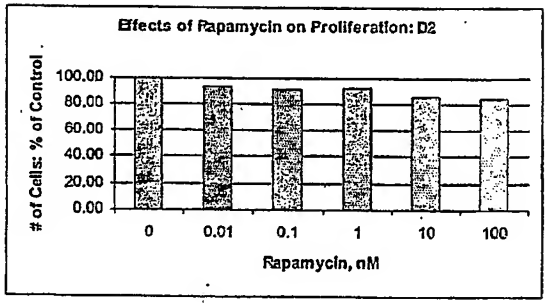


FIG. 22

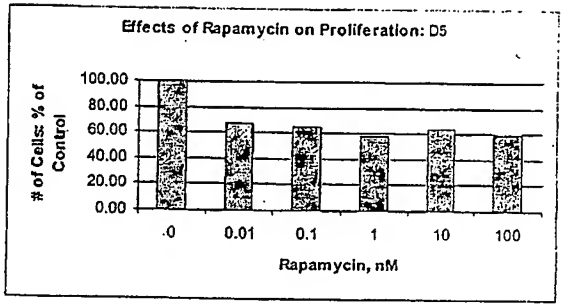


Fig. 28

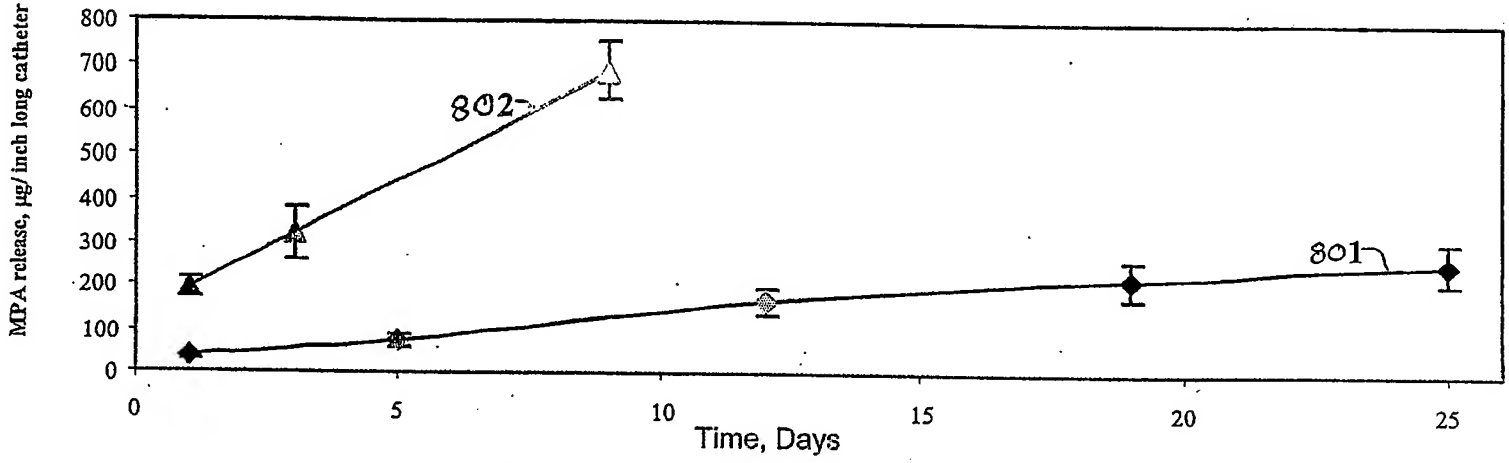


Fig. 23

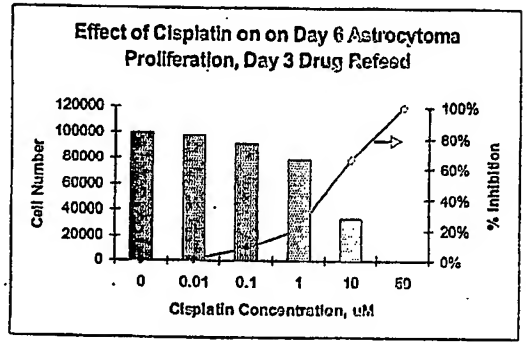
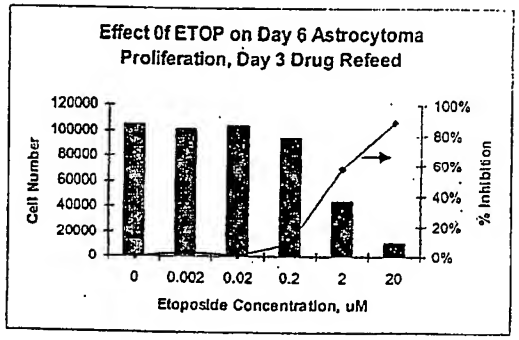


Fig. 24



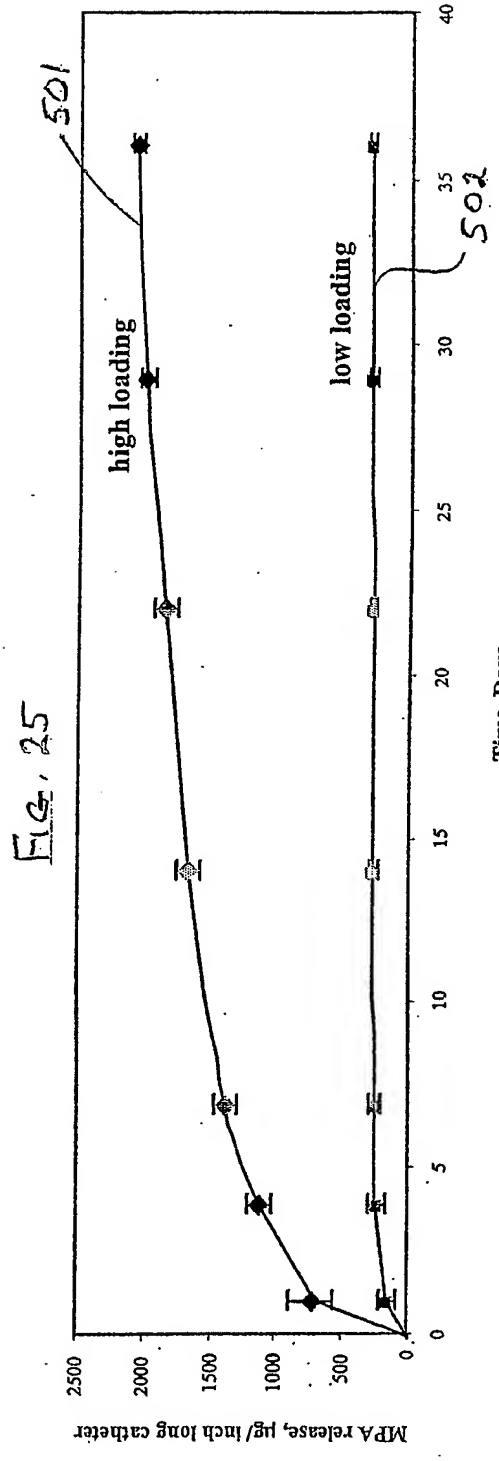

501
502
high loading
low loading
MPA release, µg/ inch long catheter
Time, Days
0
500
1000
1500
2000
2500
0
5
10
15
20
25
30
35
40

Fig. 25

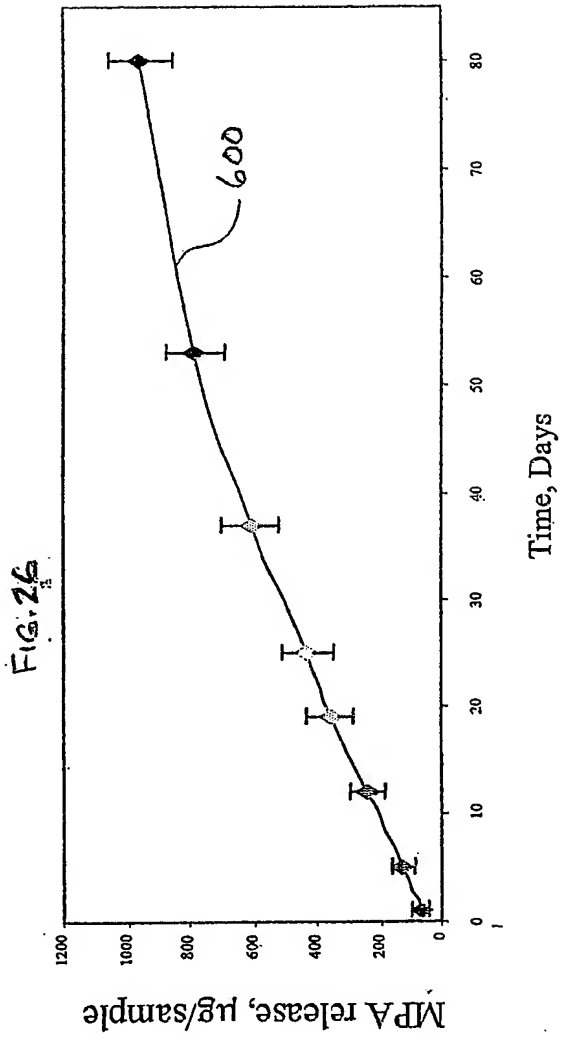

600
MPA release, µg/sample
Time, Days
0
200
400
600
800
1000
1200
0
10
20
30
40
50
60
70
80

Fig. 26

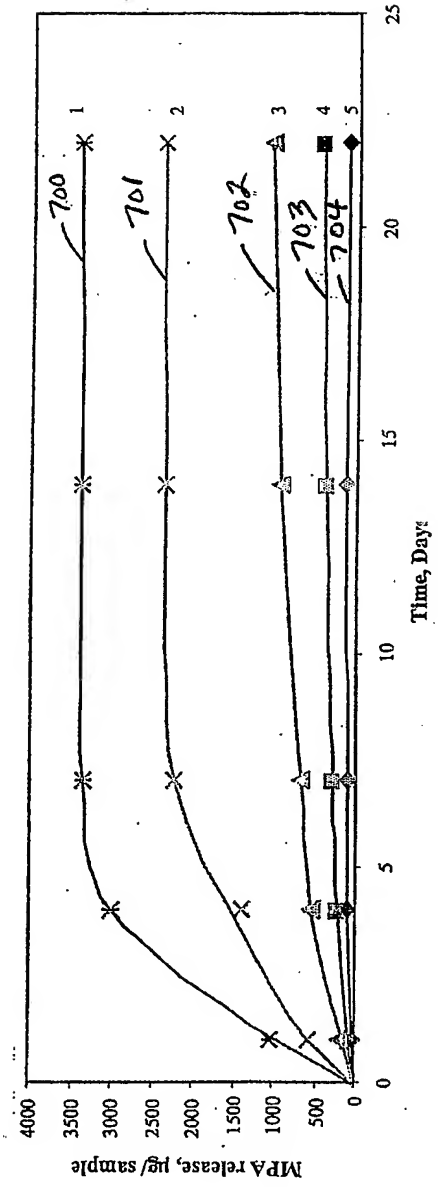
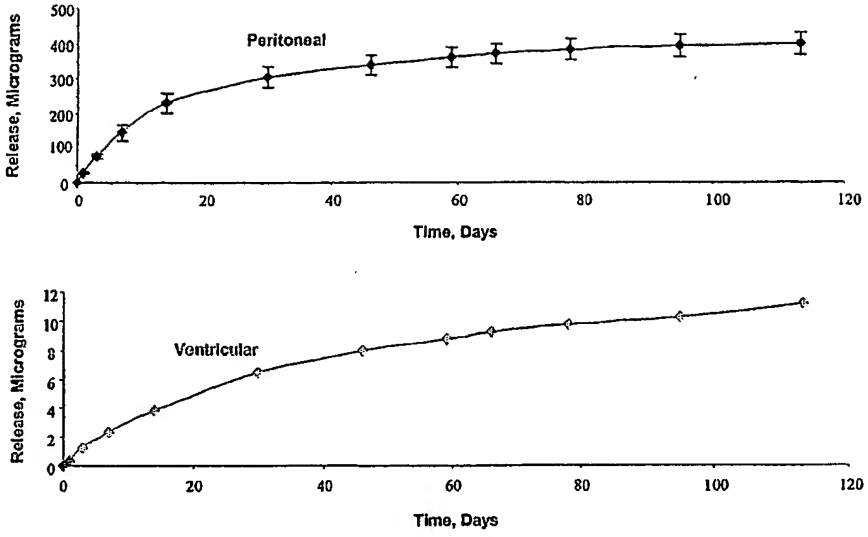

MPA release, pg/ sample
4000
3500
3000
2500
2000
1500
1000
500
0
0
5
10
15
20
25
Time, Days
1
2
3
4
5
700
701
702
703
704

FIG. 27



In-vitro release of RAPA from silicone catheters of different sizes.

Figure 29